in part (i), and then (iii) comparing the level of activation of the G-protein measured in part (i) with the level of activation of the G-protein measured in part (ii), wherein a lower level of activated G-protein in the presence of the test inhibitor has a positive correlation with an ability of the test inhibitor to inhibit the perception of a bitter taste associated with the tastant.

63. (amended) A method for identifying a bitter tastant comprising

(i) contacting a taste receptor with a G-protein, selected from the group consisting of transducin and gustducin, and a test tastant, under conditions suitable for activation of the G-protein by the test tastant, and measuring the level of G-protein activation; (ii) in a separate experiment, contacting a taste receptor with a G-protein selected from the group consisting of transducin and gustducin, the test tastant, and a bitterness inhibitor, and measuring the level of G-protein activation, where the G-protein is the same as that used in part (i), and then (iii) comparing the level of activation of the G-protein measured in part (i) with the level of activation of the G-protein measured in part (ii), wherein a lower level of activated G-protein in the presence of the bitterness inhibitor has a positive correlation with an ability of the test tastant to elicit the perception of a bitter taste.

REMARKS

Claims 1-63 are currently pending before the Examiner. Claim 1 is rejected under 35 U.S.C. §112, second paragraph. Claims 1-31, 34, 37, 39, 40, 41, 44, 47, 49-52, 55, 58, and 60-62 are rejected under 35 U.S.C. §103(a). Applicants have amended Claim 1 to more particularly point out and distinctly claim the invention. No new matter is

introduced by the amended claim and the claim is fully supported by the instant specification. For reasons set forth below, Applicants request that the rejections be withdrawn and the pending claims be allowed to issue.

1. The Invention is Claimed as Required by 35 U.S.C. §112

Claim 1 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. According to the Examiner, the claim as written is ambiguous because it is unclear what Applicant intends by the phrase "the conditions are essentially the same."

Applicants have amended Claims 1, 12, 19, 26, and 63 to indicate that the experimental conditions to be used in step (ii) of the claimed method are "conditions suitable for activation of the G-protein by the bitter tastant." The language of step (ii) as amended conforms to the language used in step (i) of the claim.

In view of the amendments to the claims, Applicants request that the rejections under 35 U.S.C. §112, second paragraph, be withdrawn.

2. The Rejections Under 35 U.S.C. §103, Should be Withdrawn

Claims 1-31, 34, 37, 39, 40, 41, 44, 47, 49-52, 55, 58, and 60-62 are rejected under 35 U.S.C. § 103, as being unpatentable over McLaughlin et al., (1993, Ciba Foundation Symposium 179:186-200; "McLaughlin") in view of Naim et al., (1994, Biochem. J. 297;451-454; "Naim"), Ruiz-Avila et al., (1995, Nature 376:80-85;"Ruiz-Avila"); Spielman (1998, J. Dent. Res. 77:539-544; "Spielman") and Boughter et al., (1997, J. Neuroscience 17:2852-2858; "Boughter").

The Examiner alleges that McLaughlin discloses the bitter compound denatonium and that it raises the intracellular calcium concentration in rat taste cells by a G-protein mediated increase in inositol triphosphate. Furthermore, the reference is said to disclose that transducin and gustducin both play roles in bitter taste transduction to stimulate bitter receptors which may activate transducin and/or gustducin. The Examiner maintains that Naim discloses amphipilic sweeteners and a bitter compound, quinine, which activate transducin and other G-proteins. Ruiz-Avila is said to disclose the coupling of a bitter compound, denatonium, to taste cell receptors which result in the activation of transducin. Spielman discloses gustducin and its roles in taste. In particular, a mechanism of gustducin mediated bitter taste signal transduction is disclosed wherein the bitter stimulant denatonium activates a cell surface receptor that is coupled to gustducin. Boughter is said to disclose differential expression of α-gustducin in taste bud population of rats and hamsters.

According to the Examiner, it would have been obvious to modify the invention of McLauglin et al. using the teachings of Naim, Ruiz-Avila, Spielman and Boughter and generate *in vivo* compositions and methods thereof for identifying a bitter taste inhibitor, and the steps set forth in the methods of identifying a bitter taste inhibitor because (i) McLauglin discloses gustducin and transducin and proposed mechanisms for bitter taste transduction; (ii) Naim discloses the use of sweeteners and a bitter tastant (quinine) which activate transducin; (iii) Ruiz-Avila disclose the bitter compound denatonium which activates transducin and the use of trypsin sensitivity to monitor activation of transducin by rhollopsin; Spielman discloses that various gustducin and other bitter taste transduction models are known in the art; and Boughter discloses that transduction of

sweet and bitter tasting substances are known to involve G-proteins. According to the Examiner, it would have been obvious to one of ordinary skill in the art to utilize the steps of the independent method claims and compare the G-protein levels to determine which compounds inhibit bitter because in the cited references, compounds were tested and it was determined which substances resulted in enhanced G-protein levels.

A finding of obviousness under §103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In re O'Farrell 853 F.2d 894, 903 (Fed. Cir. 1988).

Applicants assert that the claims are non-obvious over the references cited by the Examiner because the references only disclose that G-proteins, and in particular gustducin and transducin, are involved in the signal transduction of bitter taste. The references fail to disclose a crucial aspect of the present invention, namely that adenosine monophosphate, and its structural homologs, inhibit bitter tastant mediated G-protein activation. Prior to Applicants' invention, it was not known that adenosine monophosphate and analogs thereof, could specifically inhibit bitter taste through inhibition of G-protein activation. Indeed as set forth in Figure 5 of McLaughlin and Figure 1 of Spielman, cAMP is converted into AMP in response to G-protein mediated bitter taste signal transduction, *i.e.*, the levels of AMP are increased in response to a bitter

tastant. Most significantly, this is a **downstream** event resulting from activation of α-gustducin and α-transducin. Applicants maintain that given this result, one skilled in the art simply would not have expected that adenosine monophosphate, or structural homologs thereof, could function upstream in the signal transduction pathway to inhibit bitter taste through inhibition of G-protein activation. Accordingly, the claims are non-obvious over the cited references, so that the rejection should be removed.

For all the foregoing reasons, the cited references do not render the claims obvious, so that the rejection should be removed.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicants believe that the invention described and defined by the amended claims is patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Attached hereto as **APPENDIX A** is a marked-up version of the changes made to the claims by the current amendment.

Respectfully submitted,

Dated: March 8, 2002

Carmella L. Stephens

Lisa B. Kole
Patent Office Reg. No. 35,225
Carmella L. Stephens
Patent Office Reg. No. 41,328
BAKER BOTTS L.L.P.
30 Rockefeller Plaza
New York, New York 10112-0228

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (Amended) A method for identifying an inhibitor of bitter taste comprising (i) contacting a taste receptor with a G-protein, selected from the group consisting of transducin and gustducin, and a bitter tastant, under conditions suitable for activation of the G-protein by the bitter tastant, and measuring the level of G-protein activation; (ii) in a separate experiment, contacting a taste receptor with a G-protein selected from the group consisting of transducin and gustducin, the bitter tastant, and a test inhibitor under conditions suitable for activation of the G-protein by the bitter tastant, and measuring the level of G-protein activation, where the G-protein is the same as that used in part (i), where the conditions are essentially the same as that used in part (i), and where the test inhibitor is a structural homolog of adenosine monophosphate; and then (iii) comparing the level of activation of the G-protein measured in part (i) with the level of activation of the G-protein measured in part (ii), wherein a lower level of activated G-protein in the presence of the test inhibitor has a positive correlation with an ability of the test inhibitor to inhibit the perception of a bitter taste associated with the tastant.

12. (amended) A method for identifying an inhibitor of bitter taste comprising (i) contacting, *in vitro*, a taste receptor with a solution comprising a G-protein selected from the group consisting of transducin and gustducin, and a bitter tastant, under conditions suitable for activation of the G-protein by the bitter tastant, and

measuring the level of G-protein activation; (ii) in a separate experiment, contacting a taste receptor with a solution comprising a G-protein selected from the group consisting of transducin and gustducin, the bitter tastant, and a test inhibitor, and measuring the level of G-protein activation, where the G-protein is the same as that used in part (i), where the conditions are essentially the same as that used in part (i), and where the test inhibitor is a structural homolog of adenosine monophosphate; and then (iii) comparing the level of activation of the G-protein measured in part (i) with the level of activation of the G-protein measured in part (ii), wherein a lower level of activated G-protein in the presence of the test inhibitor has a positive correlation with an ability of the test inhibitor to inhibit the perception of a bitter taste associated with the tastant.

19. (amended) A method for identifying an inhibitor of bitter taste comprising (i) contacting, *in vitro*, a taste receptor with a solution comprising a G-protein selected from the group consisting of transducin and gustducin, and a bitter tastant, under conditions suitable for activation of the G-protein by the bitter tastant, and measuring the level of G-protein activation; (ii) in a separate experiment, contacting a taste receptor with a solution comprising a G-protein selected from the group consisting of transducin and gustducin, the bitter tastant, and a test inhibitor, and measuring the level of G-protein activation, where the G-protein is the same as that used in part (i), where the conditions are essentially the same as that used in part (i), and where the test inhibitor is not a peptide; and then (iii) comparing the level of activation of the G-protein measured in part (i) with the level of activation of the G-protein measured in part (ii), wherein a lower level of activated G-protein in the presence of the test inhibitor has a

positive correlation with an ability of the test inhibitor to inhibit the perception of a bitter taste associated with the tastant.

26. (amended) A method for identifying an inhibitor of bitter taste *in vivo* comprising

(i) contacting a taste receptor with a G-protein, selected from the group consisting of transducin and gustducin, and a bitter tastant, under conditions suitable for activation of the G-protein by the bitter tastant, and measuring the level of G-protein activation; (ii) in a separate experiment, contacting a taste receptor with a G-protein selected from the group consisting of transducin and gustducin, the bitter tastant, and a test inhibitor, and measuring the level of G-protein activation, where the G-protein is the same as that used in part (i), where the conditions are essentially the same as that used in part (i), and then (iii) comparing the level of activation of the G-protein measured in part (i) with the level of activation of the G-protein measured in part (ii), wherein a lower level of activated G-protein in the presence of the test inhibitor has a positive correlation with an ability of the test inhibitor to inhibit the perception of a bitter taste associated with the tastant.

63. (amended) A method for identifying a bitter tastant comprising

(i) contacting a taste receptor with a G-protein, selected from the group consisting of transducin and gustducin, and a test tastant, under conditions suitable for activation of the G-protein by the test tastant, and measuring the level of G-protein activation; (ii) in a separate experiment, contacting a taste receptor with a G-protein selected from the group consisting of transducin and gustducin, the test tastant, and a bitterness inhibitor, and

measuring the level of G-protein activation, where the G-protein is the same as that used in part (i), where the conditions are essentially the same as that used in part (i), and then (iii) comparing the level of activation of the G-protein measured in part (i) with the level of activation of the G-protein measured in part (ii), wherein a lower level of activated G-protein in the presence of the bitterness inhibitor has a positive correlation with an ability of the test tastant to elicit the perception of a bitter taste.